In the Claims:

Please replace all prior versions and listings of claims with the amended claims as follows:

1. (**Currently amended**) A computer-based method for generating 3-D structural models of complex formation between a query ligand and a target macromolecule, the method comprising:

a) providing a structural model of a query ligand and a structural model of a target macromolecule; wherein the structural model of the query ligand is based on data from X-ray crystallography or NMR spectroscopy, and the structural model of the target macromolecule is based on data from X-ray crystallography;

b) identifying a substructure of the query ligand;

c) identifying comparison ligands in a set of 3-D structural models that each share an identical substructure with the query ligand, wherein each 3-D structural model comprises a comparison ligand and a comparison macromolecule, and wherein the comparison macromolecule has structural features homologous to the target macromolecule of 20% or greater nucleic acid and/or amino acid homology;

d) mapping spatial relationships between the substructure atoms of the query ligand and a comparison ligand identified in c) such that corresponding atoms are identified;

e) assigning atomic coordinates to the corresponding atoms of the query ligand;

f) generating and displaying ~~diplsying~~ one or more output models, each model comprising a 3-D structural model of the query ligand substructure and the target macromolecule, wherein the 3-D model of the query ligand substructure comprises the atomic coordinates of the query ligand from step (e).

2. (**Original**) The method of claim 1, wherein the query ligand is less than 1000 Daltons MW.

3. (**Original**) The method of claim 1, wherein the query ligand is an inhibitor of the target macromolecule.

4. (**Original**) The method of claim 1, wherein the query ligand is an inhibitor of the comparison macromolecule.

5. (**Previously presented**) The method of claim 1, wherein the output models comprise models in which atoms in addition to those identified as sharing an identical substructure of the query ligand are represented.

6. (**Original**) The method of claim 1, wherein a plurality of query ligands are provided.

7. (**Previously presented**) The method of claim 1, wherein the substructure of the query ligand identified in b) comprises 2-D structural information.

8. (**Original**) The method of claim 7, wherein the substructure comprises a framework.

9. (**Currently amended**) The method of claim 8, wherein the framework comprises cyclic portions ~~atoms~~ of the query ligand, acyclic atoms that connect the cyclic portions, and sp^2-hybridized oxygen atoms connected to the cyclic and acyclic portions ~~atoms~~.

10. (**Previously presented**) The method of claim 7, wherein the substructure comprises a substructure in which at least 5, 7, or 10 atoms in each ligand are identical in the comparison ligand(s).

11. (**Previously presented**) The method of claim 1, wherein the substructure of the query ligand identified in b) comprises 3-D structural information.

12. (**Previously presented**) The method of claim 1, wherein the substructure of the query ligand identified in b) comprises a pharmacophore.

13. (**Previously presented**) The method of claim 12, wherein identifying the substructure of the query ligand comprising a pharmacophore comprises identifying comparison ligand atoms which form hydrogen-bonds with a macromolecule of interest.

14. (**Original**) The method of claim 13, wherein the macromolecule of interest is the comparison macromolecule.

15. (**Original**) The method of claim 1, wherein the target macromolecule and the comparison macromolecule are identical.

16. (**Original**) The method of claim 1, further comprising refining the output models.

17. (**Original**) The method of claim 1, wherein the target macromolecule is a polypeptide or a nucleic acid.

18. (**Original**) The method of claim 16, wherein the refining comprises performing rigid body minimization or minimization with flexible ligand sidechains.

19. (**Original**) The method of claim 17, wherein each output model comprises the 3-D spatial positions of amino acid backbone C and N atoms of the target macromolecule.

20. (**Original**) The method of claim 19, wherein each output model comprises the 3-D spatial positions of amino acid backbone Cα atoms of the target macromolecule.

21. (**Original**) The method of claim 17, wherein each output model comprises the 3-D spatial positions of amino acid sidechain C, N, S, and O atoms of the target macromolecule.

22. (**Original**) The method of claim 17, wherein each output model comprises the 3-D spatial positions of H atoms of the target macromolecule.

23. (**Original**) The method of claim 22, wherein each output model comprises the 3-D spatial positions of polar H atoms.

24. (**Original**) The method of claim 6, further comprising evaluating each output model of the plurality.

25. (**Previously presented**) The method of claim 24, wherein the evaluating comprises determining one or more of lipophilic interactions, hydrogen bonding, repulsion, and intramolecular strain energy undergone by the ligand to provide for binding between the substructure of the query ligand of b) and the target macromolecule.

26. (**Original**) The method of claim 25, further comprising assigning a score to each output model.

27. (**Previously presented**) The method of claim 26, further comprising obtaining physical samples comprising a subset of the query ligands, wherein the each of the ligands of the subset are assigned a preselected score, and wherein the samples are obtained based on an evaluation of the preselected score.

28. (**Original**) The method of claim 27, further comprising evaluating the binding of the ligands of the subset to the target macromolecule.

29. (**Original**) The method of claim 1, wherein the set of 3-D structural models is contained in a database.

30. (**Currently amended**) An apparatus comprising:

a) a memory that stores executable instructions for generating 3-D structural models of complex formation between a query ligand and a target macromolecule, and

b) a processor that executes the instructions to:

i) provide a structural model of a query ligand and a target macromolecule;

ii) identify a substructure of the query ligand;

iii) identify comparison ligands in a set of 3-D structural models that each share an identical substructure with the query ligand, wherein each 3-D structural model comprises a comparison ligand and a comparison macromolecule, and wherein the comparison macromolecule has structural features homologous to the target macromolecule <u>of 20% or greater nucleic acid and/or amino acid homology</u>;

iv) map spatial relationships between the substructure atoms of the query ligand and a comparison ligand identified in iii) such that corresponding atoms are identified;

v) assign atomic coordinates to the corresponding atoms of the query ligand;

vi) generate and ~~diplay~~ <u>display</u> one or more output models, each model comprising a 3-D structural model of the query ligand substructure and the target macromolecule, wherein the 3-D model of the query ligand substructure comprises the atomic coordinates of the query ligand from step (v).

31. (**Currently amended**) An article comprising machine-readable media that stores executable instructions for generating 3-D structural models of complex formation between a query ligand and a target macromolecule, the instructions causing a machine to:

a) provide a structural model of a query ligand and a target macromolecule;

b) identify a substructure of the query ligand;

c) identify comparison ligands in a set of 3-D structural models that each share an identical substructure with the query ligand, wherein each 3-D structural model comprises a comparison ligand and a comparison macromolecule, and wherein the comparison macromolecule has structural features homologous to the target macromolecule of 20% or greater nucleic acid and/or amino acid homology;

d) map spatial relationships between the substructure atoms of the query ligand and a comparison ligand identified in c) such that corresponding atoms are identified;

e) assign atomic coordinates to the corresponding atoms of the query ligand;

f) generate and ~~diplay~~ display one or more output models, each model comprising a 3-D structural model of the query ligand substructure and the target macromolecule, wherein the 3-D model of the query ligand substructure comprises the atomic coordinates of the query ligand from step (e).

32. (**Withdrawn**) A database of ligand-protein structure models, the database comprising a plurality of records, each record comprising information representing 3-D spatial positions of atoms in a protein and atoms in a ligand that physically interacts with the protein, wherein the database includes at least two classes of records:

a) a first class for which the 3-D spatial positions of atoms of each model are determined by a physical observation; and

b) a second class for which the 3-D spatial positions of atoms of each model of the set are inferred by the following steps:

i) identifying models from the first class that comprise a ligand having a substructure identical to a query ligand, and having a protein that comprises structural features homologous to a target protein;

ii) mapping spatial relationships between the substructure atoms of the query ligand and the comparison ligand such that corresponding atoms are identified;

iii) assigning atomic coordinates to the corresponding atoms of the query ligand;

iv) generating one or more output models, each model comprising a 3-D structural model of the query ligand substructure and the target macromolecule, wherein the 3-D model of the query ligand substructure comprises the atomic coordinates of the query ligand from step (iv).

33. (**Withdrawn**) The database of claim 32, further comprising a third class of records, for which the 3-D spatial positions of atoms of each model of the set are inferred by the following steps:

vi) providing the output models of the second class;

vii) modifying the substructure to comprise one or more additional atoms of the query ligand.

34. (**Currently amended**) A computer-based method for generating 3-D structural models of complex formation between a test ligand and a target macromolecule, the method comprising:

a) providing a 3-D structural model of a ligand and a target macromolecule;

b) identifying a substructure of the ligand;

c) identifying test ligands in a set of structural models that each share an identical substructure with the ligand of step a) ~~compound~~;

d) mapping spatial relationships between the substructure atoms of the ligand and a test ligand identified in c) such that corresponding atoms of a test ligand identified in c) are identified;

e) assigning atomic coordinates to the corresponding atoms of the test ligand;

f) generating and diplaying one or more output models, each model comprising a 3-D structural model of the test ligand and the target macromolecule, wherein the 3-D model of the test ligand comprises the atomic coordinates of the test ligand from step (e), thereby modeling complex formation between a test ligand and a target macromolecule.